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IN THE U.S. PATENT AND TRADEMARK OFFICE

Inventor	Janos KREIDL (deceased) et al	
Patent App.	10/667,201	
Filed	22 September 2003	Conf. No. 7183
For	PROCESS FOR PREPARING MONOHYDRATE AND CRYSTAL MODIFICATION	
Art Unit	1626	Examiner Stockton, L

Hon. Commissioner of Patents
Box 1450
Alexandria, VA 22313-1450

COMMUNICATION

A Declaration Under 37 CFR 1.132 is enclosed herewith along with a Curriculum Vitae signed by Laszlo Czibula.

Respectfully submitted,
The Firm of Karl F. Ross P.C.

Jonathan Myers, Reg. No. 26,963
Attorney for Applicant

er
January 27, 2006
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Enclosures

22631

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Inventor	Janos KREIDL (deceased) et al	
Patent App.	10/667,201	
Filed	**22 September 2003**	Conf. No. **7183**
For	**PROCESS FOR PREPARING MONOHYDRATE AND CRYSTAL MODIFICATIONS OF FLUCONAZOLE**	
Art Unit	**1626**	**Examiner Stockton, L**

Hon. Commissioner of Patents
Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 CFR 1.132

I, Laszlo Czibula, a citizen of Hungary, residing at Gergely u. 48, Budapest, Hungary, declare as follows:

THAT I have a number of years of experience in the synthesis of organic compounds as well as in the analysis of organic compounds;

THAT my full curriculum vitae may be attached hereto;

THAT I am an Applicant in US Patent Application Serial No. 10/667,201 filed 22 September 2003 and directed to PROCESS FOR PREPARING MONOHYDRATE AND CRYSTAL MODIFICATIONS OF FLUCONAZOLE;

THAT in order to establish that the fluconazole monohydrate and the anhydrous fluconazole obtained according to the present invention are obtained in surprisingly high purity, I have either personally conducted or supervised the carrying out of the following tests:

TESTS

The starting material as well as fluconazole monohydrate and anhydrous fluconazole were prepared according to the following examples:

EXAMPLE A

2-(2,4-Difluorophenyl)-1,3-bis(1,2,4-triazol-1-yl)-2-(trimethylsilyloxy)propane, a starting material for the present process was prepared according to US Patent 5,707,976.

Under nitrogen atmosphere 11.85 g (0.05 moles) of 1,2-epoxy-2-(2,4-difluorophenyl)-3-(1,2,4-triazol-1-yl) propane (prepared in accordance with the process described in GB patent specification No. 2,099,818 A) are reacted with 9.16 g (0.065 moles) of 1-(trimethylsilyl)-1,2,4-triazole and 0.01 g (0.12 mmoles) of 1,2,4-triazol-1-yl sodium in 100 ml of dimethyl formamide for 1 hour at 80°C. The reaction mixture is cooled to room temperature, neutralized with glacial acetic acid and mixed with 500 ml of water. The aqueous mixture is extracted twice with 100 ml of dichloromethane each. The combined extracts are washed three times with 100 ml of water each, dried over water-free sodium sulfate and evaporated to solvent-free in vacuo. The evaporation residue is crystallized from 60 ml of n-hexane containing 5% by volume of ethyl acetate. 16.065 g (85%) of the title compound are obtained; m.p.: 69°-71° C.

EXAMPLE 1

2-(2,4-Difluorophenyl)-1,3-bis(1,2,4-triazole-1-yl)-propane-2-ol monohydrate

A mixture of 7.50 g (0.02 mol) of 2-(2,4-difluorophenyl)-1,3-bis(1,2,4-triazole-1-yl)-2-(trimethylsilyloxy)propane, 25 ml of methanol, 2 ml of water and 1.0 ml of concd. hydrochloric acid was stirred at 30 °C for 1 h. The reaction mixture was concentrated to a

volume of 10 ml and after adding 50 ml of water the pH of the hot solution was adjusted to 8 with 10 % aqueous sodium hydroxide. After cooling the precipitated crystals were filtered off, and dried at 40 °C until the weight was constant to yield 6.06 g (93.5 %) of the title compound. M.p.: 139-140 °C.

EXAMPLE 2

Synthesis of crystal modification I of fluconazole

A mixture of 7.5 g (0.02 mol) of 2-(2,4-difluorophenyl)-1,3-bis(1,2,4-triazole-1-yl)-2-(trimethylsilyloxy)propane, 40 ml of methanol, 3 ml of water and 0.1 g of sodium hydroxide was stirred at room temperature for 1 h. After adding 300 ml of water the solution was concentrated to a volume of 50 ml with vacuum distillation. The obtained suspension was cooled to 0 °C and filtered. The obtained product was 6.12 g, water content was 11.5 %. After drying at 80 °C 5.35 g of title compound was obtained. Yield: 87.4 %. Mp.: 139-141 °C.

HPLC Analysis

We carried out HPLC analysis on each of the products of Examples A, 1 and 2 with respect to the desired products as well as impurities in the product.. We checked each product for the following impurities:

Impurity A 2(2,4-difluorophenyl-1-(1H-1,2,4-triazol-1-yl)-3-(4H-1,2,4-triazol-4-yl)-2-propanol (isofluconazole) or its corresponding O-trimethylsilylether

Impurity B 2-[2-fluoro-4-(1H-1,2,4-triazol-1-yl)phenyl]-1,3-bis(1H-1,2,4-triazol-1-yl)-2-propanol or its corresponding O-trimethylsilylether

Impurity C 1,1'-(1,3-phenylene)di(1H-1,2,4-triazole)

These three impurities are listed on page 22 of Pharmeuropa 10/1, 20 to 22 (1998) as the three principal impurities contained in fluconazole but Impurioties A and B asre listed only as the free alchol with no mention of the corresponding O-trimethylsilyl ethers. The limits of each of these impurities are also given in this reference. In addition to preparing the O-trimethyl silyl ether of fluconazole of Example A, fluconazole monohydrate of Example 1 and the anhydrous fluconazole of Example 2 hereinabove, we also synthesized each of the three impurities: Impurities A, B and C. By using HPLC we determined the quantities of each of the three impurities in the O-trimethylsilyl-fluconazole starting material as prepared in Example A, the fluconazole monohydrate as prepared in Example 2 and the anhydrous fluconazole as prepared in Example 3. The attached three HPLC chromatograms 1,2 and 3, respectively, are the O-trimethylsilyl-fluconazole of Example A, [Fluk051205-01]; fluconazole monohydrate of Example 1, [Fluk05120601),and anhydrous fluconazole (Fluconazole anhydrous Form I) of Example 2, {Fluk05120601}.

On the chromatogram A of the O-trimethyl silyl-fluconazole starting material prepared according to Example A above, the peaks at RT = 5.452 show the O-trimethylsilyl ether of Impurity A and at RT = 5.958 the O-trimethyl-silyl ether of Impurity B set forth in the Pharmeuropa. No evidence of Impurity C was found.

On the chromatograms 1 and 2 of the fluconazole monohydrate and anhydrous fluconazole prepared according to Examples 1 and 2 above, the peaks at about RT 7.7 show Impurity B and at about RT 8.3 show Impurity A as set forth in the Pharmeuropa. No evidence of Impurity C was found.

The large peaks on each of the chromatograms show the mean compounds, that is the desired products of Examples A, 1 and 2, respectively.

The given values in the column "Area%" are the same as the mass% , but by the Impurity B and by its silyl derivative this value must be divided by 10 , as this compound due to its very strong conjugation provides a signal 10 times higher.

The above data show, that the obtained fluconazole monohydrate and anhydrous fluconazole (as in Fluconazole Crystal Modifications I and II) have one-tenth the quantity of impurities than those given for fluconazole monohydrate and anhydrous fluconazole in the Pharmeuropa ;

THAT I conclude based upon the data presented above that the present process starting with the hydrolysis as set forth in Example 1 above of the silyl ethers of US Patent 5,707,976 as prepared according to Example A above enables one to obtain fluconazole monohydrate and anhydrous fluconazole in a surprisingly high purity;

THAT I am aware of no information inconsistent with that presented above or which would lead one to a contrary conclusion; and

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 USC 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

23. 01. 2006. Laszlo Czibula

Date

Curriculum Vitae

I, Dr. László Czibula, declare and say:

That I am a citizen of Hungary and I reside at 48. Gergely str. 1103 Budapest, Hungary;

That I was graduated in 1972 from Technical University of Sciencas located in Budapest with a Master of Science Degree in Medicinal Chemistry. I was also graduated in 1977 from Technical University located in Budapest with a Doctor's Degree in Alkaloid Chemistry.

That since 1972 I have been working for Chemical Works of Gedeon Richter Ltd. in the field of Organic Chemistry and Medicinal Chemistry. I have been employed by research fellow since 1972, and part of this time has been spent in this field. Since 1998 I have been manager of department in the Technological Development Department of Chemical Works of Gedeon Richter.

That I am inventor of 54 patents in the Medicinal Chemistry field, and I am the author of 6 papers in the Organic Chemistry field.

Budapest, 03 January 2006

Dr. László Czibula
1103 Budapest, Hungary
Gergely str. 48. IV/39.

Mode: Reprocessed Data
Reported On: 05-12-07 10:14:15
Original Results: C:\TSP\MANO2\2005FLUKONAZOLE\Data\Fluk051205-01.RES
Reprocessed Results: C:\TSP\MANO2\2005FLUKONAZOLE\Data\Fluk051205-01.RMS
Notes:
Magán ei.Flukonazol/2:30ACN+30MOH+40d.víz H:25C Fl:1.0ml/p
K-752 Szilil-Flukonazol 1.503mg/ml

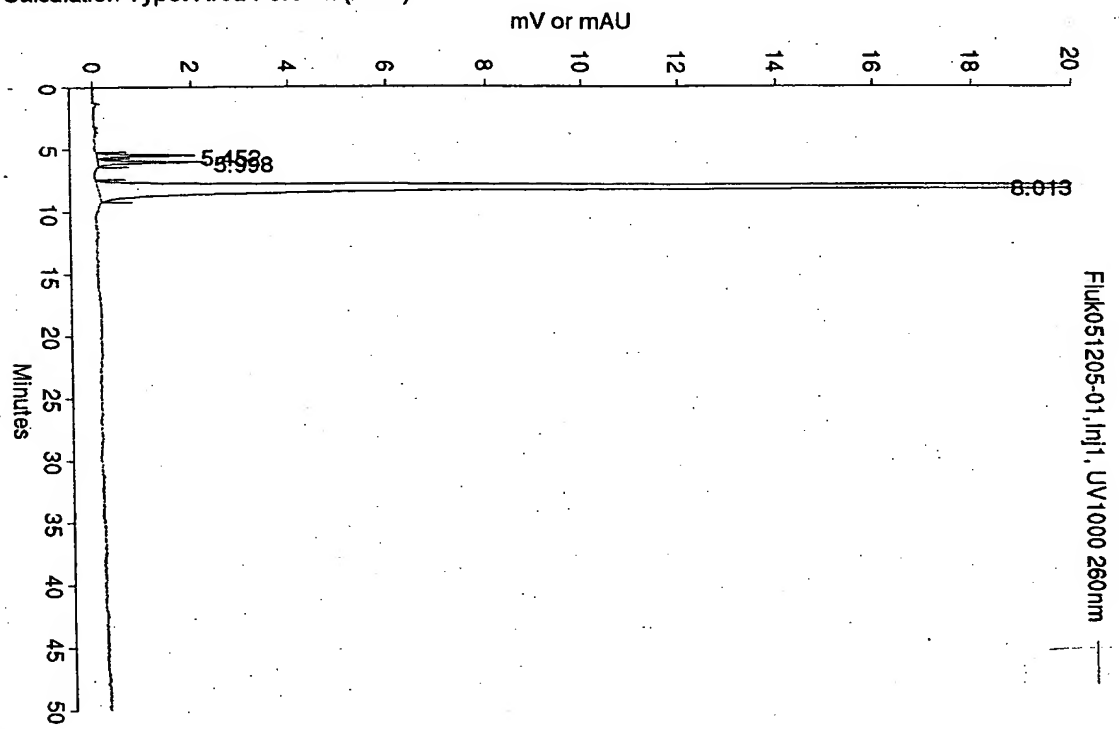
"Chromatogram A"

Analysis Report

Name: Fluk051205-01
Type: Sample
Injection Volume: 10.0 uL
Vial: 01
Injection: 1 of 1
Injected On: 05-12-05 12:04:53

Acquisition Log
Column Pressure (bar): 153
Column Temperature (C): N/A
Pump Flow Stability: 8.6
Noise (microAU): 5
Drift (microAU/min): -3e+001
Run-Time Messages: None

Signal 1: UV1000 260 nm
Calculation Type: Area Percent (Area)



Component	RT(min)	Area	Height	Area%	Peak Type
Unident0001	5.452	17444	1998	1.14	Fused → silyl-iso-fluconazole
Unident0002	5.998	23356	2232	1.53	Fused → silyl-"B"
Unident0003	8.013	1488365	110949	97.33	Resolved
Totals		1529165	115179	100.00	

System: Reprocess
Analyst: CsK
PC1000 Ver 3.0.3
Acquisition Method: C:\TSP\MANO2\2005FLUKONAZOLE\Methods\Fluk.AQM
05-12-05 10:58:20
Calculation Method: C:\TSP\Methods\Flukpr.CAM
05-12-07 08:55:06
Report Method: C:\TSP\Methods\Fluk.RPM
05-12-07 08:06:02

Mode: Reprocessed Data
Reported On: 05-12-07 09:25:58
Original Results: C:\TSP\MANO2\2005FLUKONAZOLE\Data\Fluk051206-01.RES
Reprocessed Results: C:\TSP\MANO2\2005FLUKONAZOLE\Data\Fluk051206-01.RMS
Notes:
Flukonazol/3 75ACN+50MOH+25THF+850-0.1M NH4OAC H:25C Fl:1.0 ml/p
L-700 Flukonazol monohidrát 5.004mg/ml

Chromatogram "B"

Analysis Report

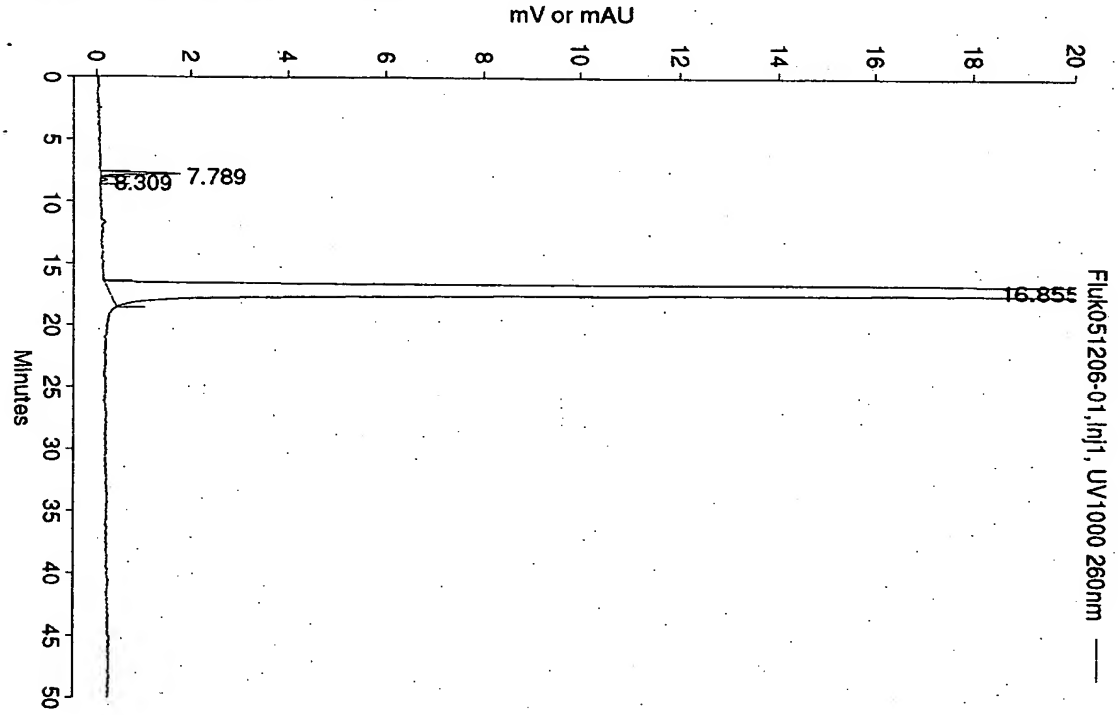
Name: Fluk051206-01
Type: Sample
Injection Volume: 10.0 uL

Vial: 01

Injection: 1 of 1
Injected On: 05-12-06 08:18:51

Acquisition Log
Column Pressure (bar): 101
Column Temperature (C): N/A
Pump Flow Stability: 2.2
Noise (microAU): 7
Drift (microAU/min): 1e+001
Run-Time Messages: None

Signal 1: UV1000 260 nm
Calculation Type: Area Percent (Area)



Component	RT(min)	Area	Height	Area%	Peak Type
Unident0001	7.789	18645	1703	0.32	Fused
Unident0002	8.309	1579	151	0.03	Fused
Unident0003	16.855	5881967	225453	99.66	Resolved
Totals		5902191	227307	100.00	

→ "B"
→ "A"

System: Reprocess
Analyst: CsK
PC1000 Ver 3.0.3
Acquisition Method: C:\TSP\MANO2\2005FLUKONAZOLE\Methods\Flukon.AQM
05-12-06 07:30:32
Calculation Method: C:\TSP\Methods\Flukon.CAM
05-12-07 09:20:52
Report Method: C:\TSP\Methods\Fluk.RPM
05-12-07 08:06:02

Mode: Reprocessed Data
Reported On: 05-12-07 10:07:48
Original Results: C:\TSP\MANO2\2005FLUKONAZOLE\Data\Fluk051206-02.RES
Reprocessed Results: C:\TSP\MANO2\2005FLUKONAZOLE\Data\Fluk051206-02.RMS
Notes:
Flukonazol/3 75ACN+50MOH+25THF+850-0.1M NH4OAC H:25C Fl:1.0 ml/p
L-700 Flukonazol anhidrát 5.002mg/ml

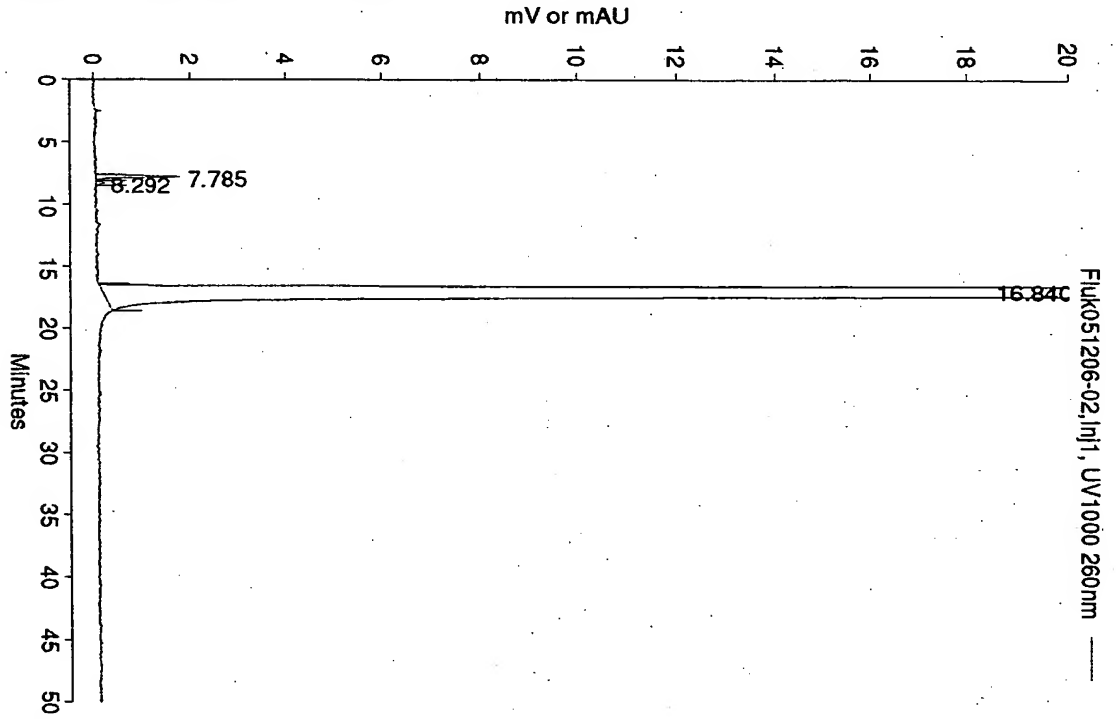
Chromatogram "C"

Analysis Report

Name: Fluk051206-02
Vial: 02
Injection: 1 of 1
Type: Sample
Injected On: 05-12-06 09:21:20
Injection Volume: 10.0 uL

Acquisition Log
Column Pressure (bar): 100
Column Temperature (C): N/A
Pump Flow Stability: 2.7
Noise (microAU): 7
Drift (microAU/min): -1e+001
Run-Time Messages: None

Signal 1: UV1000 260 nm
Calculation Type: Area Percent (Area)



Component	RT(min)	Area	Height	Area%	Peak Type
Unident0001	7.785	19438	1776	0.32	Fused
Unident0002	8.292	1614	157	0.03	Fused
Unident0003	16.840	6126882	231724	99.66	Resolved
Totals		6147934	233657	100.00	

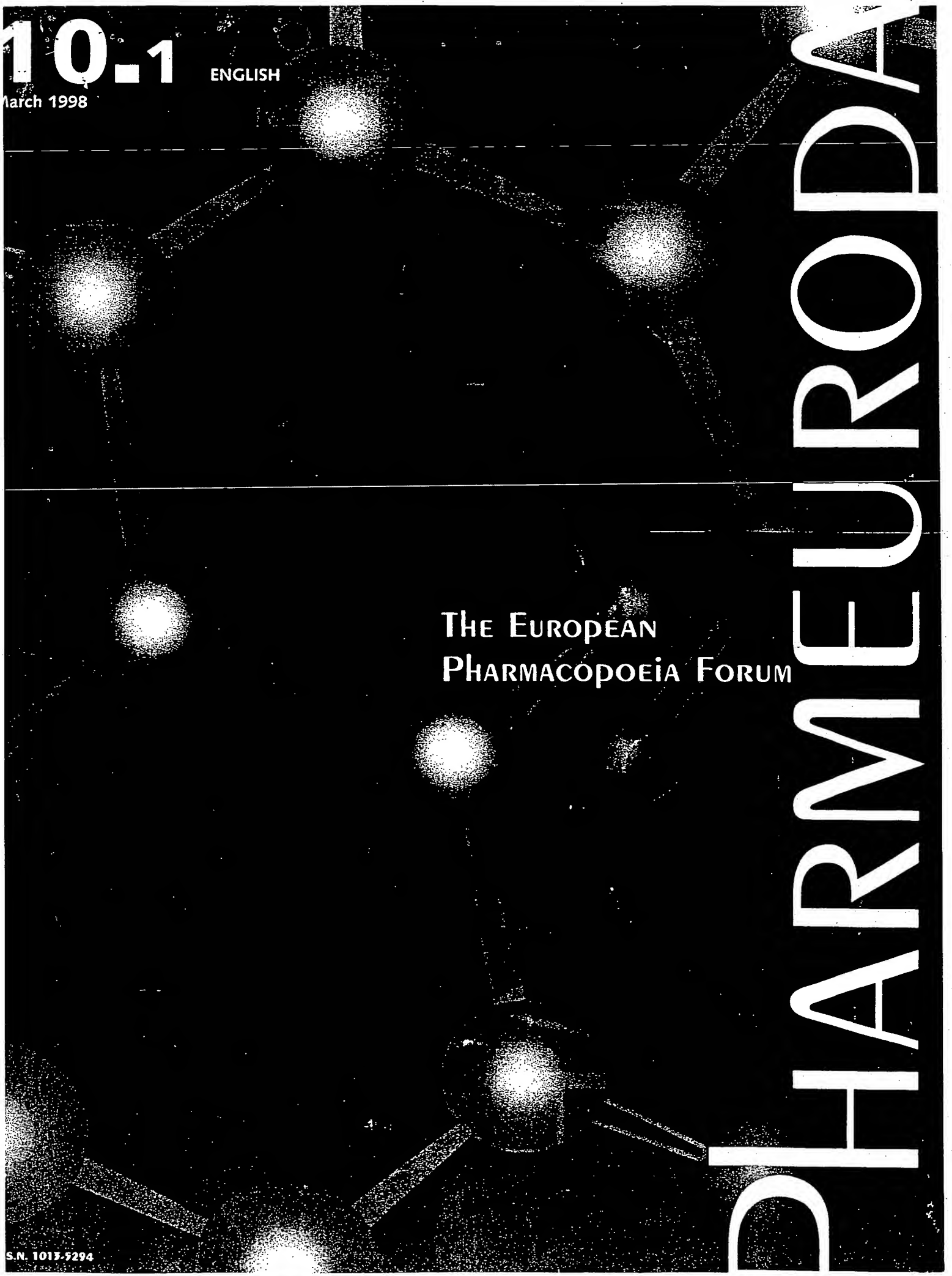
"B"
"A"

System: Reprocess
Analyst: CsK
PC1000 Ver 3.0.3
Acquisition Method: C:\TSP\MANO2\2005FLUKONAZOLE\Methods\Flukon.AQM
05-12-06 07:30:32
Calculation Method: C:\TSP\Methods\Flukonpr.CAM
05-12-07 09:59:16
Report Method: C:\TSP\Methods\Fluk.RPM
05-12-07 08:06:02

10-1 ENGLISH
March 1998

PHARMEUROPA

The European Pharmacopoeia Forum



S.N. 1017-5294

B. Examine by thin-layer chromatography (2.2.27), using a *TLC silica gel plate R* [1].

Test solution. Dissolve 1.0 g of the substance to be examined in *methylene chloride R* and dilute to 20 ml with the same solvent.

Apply to the plate 10 µl of the test solution. Develop over a path of 15 cm using a mixture of 30 volumes of *hexane R* and 70 volumes of *ether R*. Allow the plate to dry in air. Spray with a 0.1 g/l solution of *rhodamine B R* in *alcohol R* and examine in ultraviolet light at 365 nm. The chromatogram shows a spot corresponding to triacylglycerols with an R_f of about 0.9 (R_{st} 1), and spots corresponding to 1,3-diacylglycerols (R_{st} 0.7), 1,2-diacylglycerols (R_{st} 0.6) and monoacylglycerols (R_{st} 0.1).

C. It complies with the assay (monoacylglycerol content).

TESTS

Acid value (2.5.1). Not more than 3.0, determined on 1.0 g.

Iodine value (2.5.4). Not more than 3.0.

Saponification value (2.5.6). 158 to 177, determined on 2.0 g.

Free glycerol. Not more than 6.0 per cent, determined as described under Assay.

Composition of fatty acids. Examine by gas chromatography (2.4.22, *Method A* [2]). The fatty acid fraction of the substance has the following composition:

— stearic acid: 40.0 per cent to 60.0 per cent,

— sum of the contents of palmitic acid and stearic acid: not less than 90.0 per cent.

Nickel (2.2. ...) [3]. Not more than 1 ppm.

Water (2.5.12). Not more than 1.0 per cent, determined on 1.00 g by the semi-micro determination of water. Use as the solvent a mixture of equal volumes of *anhydrous methanol R* and *methylene chloride R*.

Total ash (2.4.16). Not more than 0.1 per cent, determined on 1.00 g.

ASSAY

Determine the free glycerol content and the mono-, di- and triacylglycerol contents by size-exclusion chromatography (2.2.30).

Test solution. Into a 15 ml flask, weigh about 0.2 g (m), to the nearest 0.1 mg. Add 5 ml of *tetrahydrofuran R* and shake to dissolve. Reweigh the flask and calculate the total mass of solvent and substance (M).

Reference solutions. Into four 15 ml flasks, respectively weigh, to the nearest 0.1 mg, about 10 mg, 20 mg, 40 mg and 50 mg of *glycerol R*. Add 5 ml of *tetrahydrofuran R* and shake until well mixed. Weigh the flasks again and calculate the concentration of glycerol in milligrams per gram for each reference solution.

The chromatographic procedure may be carried out using:

— a gel permeation column 0.6 m long and 7 mm in internal diameter packed with *styrene-divinylbenzene copolymer R* (particle diameter 5 µm and porosity 10 nm), [4]

— as mobile phase at a flow rate of 1 ml/min *tetrahydrofuran R*,

— a differential refractive index detector.

Inject 40 µl of each solution. When the chromatograms are recorded in the prescribed conditions, the retention times relative to glycerol are about 0.86 for the monoacylglycerols, about 0.81 for the diacylglycerols and about 0.77 for the triacylglycerols. From the calibration curve obtained with the reference solutions determine the concentration (C) in milligrams per gram of glycerol in the test solution. Calculate the percentage content of free glycerol in the substance to be examined using the following expression:

$$\frac{C \times M}{m \times 10}$$

Calculate the percentage content of mono-, di- and triacylglycerols in the substance to be examined by the normalisation procedure.

STORAGE

Store at a temperature not exceeding 18 °C (powder).

(1) Ready-to-use silica gel type 60 plates are suitable.
(2) Method in force.
(3) See Pharmeuropa 9.2.
(4) PL gel 5 µm is suitable.

PA/PH/Exp. 10B/T (96) 102 ANP

NOTE ON THE MONOGRAPH

Related substances test

The procedure routinely used by the manufacturer consists of a combination of two TLC systems with corresponding spraying. The methods were carried out by the three collaborating laboratories but the TLC plates were found to be difficult to interpret and not reproducible.

The decision was taken to try to use a HPLC method: the assay method used by the manufacturer was taken as a starting point, with only a slight change (addition of a

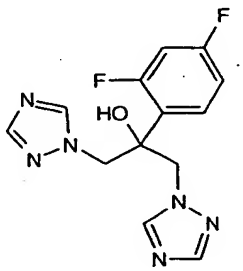
modifier, tetramethylammoniumbromide, in the solvent system) to enable the use of benzimidazole for the resolution test (due to a lack of material, the use of an impurity as CRS is not possible). The procedure allows for the separation of the three impurities from each other and from fluconazole. However, one lab did not succeed in separating impurity A from B.

The use of other methods used in the European Pharmacopoeia for compounds of the same pharmacological family did not succeed.

This monograph is presented in the new style agreed for the 4th Edition.

FLUCONAZOLE

Fluconazolum



DEFINITION

2-(2,4-difluorophenyl)-1,3-bis-(1*H*-1,2,4-triazol-1-yl)-2-propanol, $C_{13}H_{12}N_6OF_2$, M_r 306.3.

Contents: 99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance: white crystalline powder,

Solubilities: slightly soluble in water, freely soluble in methanol.

IDENTIFICATION

First identification: B.

Second identification: A, C, D.

A. Melting point (*2.2.14*): 136 °C-140 °C.

B. Infrared absorption spectrophotometry (*2.2.24*):

Comparison: fluconazole CRS.

Procedure: discs of *potassium bromide R*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in the minimum volume of *methylene chloride R*, evaporate to dryness on a water-bath and record new spectra using the residues.

C. Examine by thin layer chromatography (*2.2.27*).

Test solution. Dissolve 50 mg of the substance to be examined in *methanol R* and dilute to 5 ml with the same solvent.

Reference solution (a). Dissolve 50 mg of *fluconazole CRS* in *methanol R* and dilute to 5 ml with the same solvent.

Reference solution (b). Dilute 50 mg of *econazole CRS* and 50 mg of *fluconazole CRS* in *methanol R* and dilute to 5 ml with the same solvent.

–Plate

Coating: TLC silica gel F_{254} R,

Development: acetic acid R, water R and *methylisobutylketone R* (25:25:50).

Detection: Apply separately to the plate 10 µl of each solution. Develop over a path of 10 cm. Allow the plate to dry in air. Examine in ultraviolet light.

Performance: The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a). The test is not valid unless reference solution (b) shows two clearly separated spots.

D. Mix 90 mg of the substance to be examined with 0.30 g of *anhydrous sodium carbonate R* and ignite in a crucible until an almost white residue is obtained (normally in less than 5 min). Allow to cool and dissolve the residue in 5 ml of *dilute nitric acid R*. Filter. To a freshly prepared mixture of 0.1 ml of *alizarin s solution R* and 0.1 ml of *zirconyl nitrate solution R*, add 1.0 ml of filtrate. Mix, allow to stand for 5 min and compare the colour of the solution with that of a blank prepared in the same manner. The colour of the test solution is yellow and that of the blank is red.

TESTS

Appearance of solution. Dissolve 0.5 g in *methanol R* and dilute to 10 ml with the same solvent. The solution is clear (*2.2.1*) and colourless (*Method II, 2.2.2*).

Related substances. Examine by liquid chromatography (*2.2.29*).

Test solution. Dissolve 250.0 mg of the substance to be examined in 5ml of *methanol R* and dilute to 10.0 ml with the mobile phase.

Reference solution (a). Dilute 5.0 ml of the test solution to 100.0 ml with the mobile phase. Dilute 1.0 ml of this solution to 10.0 ml with the mobile phase.

Reference solution (b). Dissolve 5 mg of *benzimidazole R* in 4 ml of the test solution and dilute to 10 ml with the

mobile phase. Dilute 1 ml of this solution to 10 ml with the mobile phase.

–Column

Material: stainless steel.

Packing: *octadecylsilyl silica gel for chromatography R* (5 µm).

Size: L = 0.15 m, ∅ = 4.6 mm.

Elution: *acetonitrile R*, *water R* and a mixture of equal volumes of *0.05 M tetramethylammonium bromide* and *0.01 M sodium acetate* (adjusted to pH 5.0 with *acetic acid R* (100:150:750).

Flow rate: 1.0 ml/min.

–Detector

Spectrophotometer set at 261 nm.

–Chromatography

Injection volume: 20 µl.

Sensitivity: The height of the principal peak in the chromatogram obtained with reference solution (b) is at least 50 per cent of the full scale of the recorder.

Performance: Resolution of not less than 6.0, between the peaks due to benzimidazole and fluconazole.

–Limits

Correction factors: fluconazole impurity B 0.3, fluconazole impurity C 0.2.

Impurity A: Area not more than 0.6 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent).

Impurity B: Area not more than 0.6 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent).

Impurity C: Area not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent).

Any other impurity: Area not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent).

Total: Area not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent).

Disregard limit: Area not more than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

–Retention times

Substance	Approx retention time (min)
Impurity A	5
Impurity B	6
Fluconazole	8
Impurity C	16

Loss on drying (*2.2.32*). Not more than 0.5 per cent, determined on 1.000 g by drying in an oven at 100 °C to 105 °C.

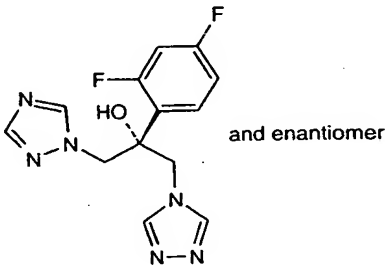
Sulphated ash (*2.4.14*). Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.125 g in 60 ml of *anhydrous acetic acid R*. Carry out the non-aqueous titration of bases (*2.2.20*). Titrate with *0.1 M perchloric acid* to the first point of inflection.

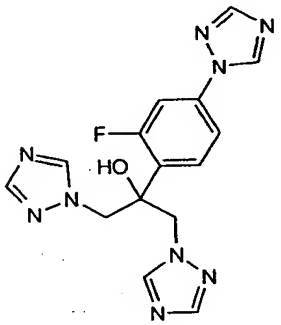
1 ml of *0.1 M perchloric acid* is equivalent to 15.32 mg of $C_{13}H_{12}N_6OF_2$.

IMPURITIES

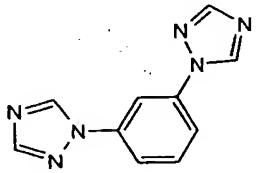


and enantiomer

A. 2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol)-1-yl)-3-(4*H*-1,2,4-triazol-4-yl)-2-propanol,



B. 2-[2-fluoro-4-(1*H*-1,2,4-triazol-1-yl)phenyl]-1,3-bis(1*H*-1,2,4-triazol-1-yl)-2-propanol,



C. 1,1′-(1,3-phenylene)di(1*H*-1,2,4-triazole).